UNITED STATES DISTRICT COURT
DISTRICT OF NEVADA

BAYER SCHERING PHARMA AG and BAYER HEALTHCARE PHARMACEUTICALS INC.,

Plaintiffs/Counter-defendants,

v.

WATSON PHARMACEUTICALS, INC., WATSON LABORATORIES, INC., and SANDOZ INC.,

Defendants/Counter-claimants.

Case No. 2:07-CV-01472-KJD-GWF
2:08-CV-00995-KJD-GWF

ORDER

Presently before the Court is Defendants/Counter-claimants' Joint Motion for Summary Judgment (#252/253). Plaintiffs filed a response in opposition (#281) to which Defendants replied (#305/306). Also before the Court is Plaintiffs' Motion for Summary Judgment of Non-obviousness of Claims 13 and 15 of United States Reissue Patent No. '564 (#254/255). Defendants filed a response in opposition (#279/280) to which Plaintiffs replied (#301/302).

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I. Regulatory Background[1]

The Federal Food, Drug, and Cosmetic Act ("FDCA"), 21 U.S.C. §§ 301 et seq., governs the sale and manufacture of prescription drugs in the United States. Any entity seeking to distribute a new prescription drug must file a New Drug Application ("NDA") with the Food and Drug Administration ("FDA"). The application must include "full reports of investigations which have been made to show whether or not such drug is safe for use and whether such drug is effective in use." 21 U.S.C. § 355(b)(1)(A). Upon approval by the FDA, a drug may be manufactured and sold in the United States. Drugs approved by the FDA under the NDA process are commonly referred to as "brand-name" drugs.

Brand-name drugs are typically protected by patents at the time of their approval by the FDA, and for a number of years thereafter. A patent holder has the exclusive right to make, use and sell the patented invention during the life of the patent. See 35 U.S.C. § 154(a). A manufacturer of a brand-name drug protected by a patent is able to sell the drug at monopoly prices.

The Drug Price Competition and Patent Term Restoration Act of 1984 ("Hatch-Waxman Act" or "Hatch-Waxman") was passed to facilitate the approval of generic versions of brand-name drugs. See 21 U.S.C. § 355. Under Hatch-Waxman, a manufacturer seeking FDA approval of a new brand-name drug must file with its NDA the patent number and expiration date of any patent which claims the drug for which the applicant submitted the application or which claims a method of using such drug and with respect to which a claim of patent infringement could reasonably be asserted if a person not licensed by the owner engaged in the manufacture, use, or sale of the drug. Id. § 355(b)(1). The brand-name drug and its associate patent or patents are then published in the "Approved Drug Products with Therapeutic Equivalence Evaluations," commonly referred to as the "Orange Book."

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1. The Court adopts the excellent description by Circuit Judge William A. Fletcher of the regulatory process created by the Hatch-Waxman Act found in Kaiser Foundation Health Plan, Inc. v. Abbott Labs., Inc., 552 F.3d 1033, 1036-38 (9th Cir. 2009).

Under Hatch-Waxman, a drug manufacturer seeking FDA approval for a generic version of a brand-name drug may file an Abbreviated New Drug Application ("ANDA") showing that its proposed generic drug is the "bioequivalent" of an already approved brand-name drug. Id. § 355(j). The ANDA shall contain, with respect to patents for the already approved brand-name drug listed in the Orange Book,

> a certification ...
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> (I) that such patent information has not been filed,
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> (II) that such patent has expired,
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> (III) of the date on which such patent will expire, or
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> (IV) that such patent is invalid or will not be infringed by the manufacture, use, or sale of the new drug for which the application is submitted[.]

Id. § 355(j)(2)(A)(vii). Such a certification is referred to as a "Paragraph I," "Paragraph II," "Paragraph III," or "Paragraph IV" certification. The first ANDA applicant for approval of a generic version of a particular brand-name drug who makes a Paragraph IV certification is guaranteed a 180-day period of exclusive distribution of the generic drug if that drug is approved by the FDA. The 180-day period begins either on the date the applicant notifies the FDA of its first "commercial marketing" of the generic drug, or on the date of the judicial decision holding the patent invalid or not infringed, whichever is earlier. Id. § 355(j)(5)(B)(iv).

An ANDA applicant who makes a Paragraph IV certification must notify the patent holder of that certification. Id. § 355(j)(2)(B). If an ANDA contains a Paragraph IV certification, FDA approval of the proposed generic drug must be "made effective immediately unless ... an action is brought for infringement of the patent that is the subject of the certification" within forty-five days of the patent holder receiving notice of the certification. Id. § 355(j)(5)(B)(iii). If a patent holder brings suit within forty-five days, FDA approval will not become effective until thirty-months after the receipt of the notice, subject to certain exceptions. Id. This thirty-month delay is commonly referred to as the "automatic stay." An exception to the thirty-month automatic stay is a final court decision

in the patent holder's infringement suit that the patent is invalid or not infringed. In the event of such a court decision, FDA approval "shall be made effective on the date on which the court enters judgment reflecting the decision" if the court decision is less than thirty months after receipt of the notice. Id. § 355(j)(5)(B)(iii)(I).

If a patent holder fails to bring an infringement suit within forty-five days of receipt of a Paragraph IV notification, it loses the right to the thirty-month automatic stay of FDA approval of the proposed generic drug. However, the patent holder does not lose the right to bring an infringement suit against the generic drug manufacturer; the patent holder simply loses the right to bring the infringement suit under Hatch-Waxman.

A patent holder who misses the forty-five day deadline for bringing a Hatch-Waxman infringement suit suffers two significant disadvantages. First, the patent holder cannot bring an infringement suit immediately upon the filing of the ANDA; it must wait until the generic drug is sold commercially. See 35 U.S.C. § 271(e)(1). See generally, Merck KGAA v. Integra Lifesciences I, Ltd., 545 U.S. 193 (2005). Second, there is no automatic stay barring the FDA from approving the generic drug. Once approved, its manufacturer may sell the generic drug during the pendency of any infringement suit brought by the patent holder.

II. Procedural History

This action was filed on November 5, 2007. On November 4, 2008, the Court consolidated 2:08-cv-0995-RLH-RJJ with this action, essentially adding Defendant Sandoz, Inc. as a party. Plaintiff Bayer Schering Pharma AG ("Bayer") owns U.S. Reissue Patent No. 37, 564 ("the '564 reissue patent") and U.S. Reissue Patent No. 37, 838 ("the '838 reissue patent")(collectively, the "Spona patents"). The Spona patents cover Bayer's oral contraceptive YAZ® ("YAZ") tablets. Defendants Watson and Sandoz filed an ANDA with the FDA for permission to market a generic version of YAZ tablets prior to the expiration of the Spona patents and made a paragraph IV certification as to '564 and '838.

On June 28, 2010, Bayer filed a motion for summary judgment asserting that there is no evidence to dispute that Defendants infringed its U.S. Reissue Patent Nos. 37,564 ("the '564 patent") and 37,838 ("the '838 patent"). Defendants did not dispute that their New Drug Applications ("NDAs") which caused the initiation of this lawsuit infringe the '564 patent and acquiesced to the granting of Bayer's motion for summary judgment of infringement of this patent. However, Defendants did dispute infringement of the '838 patent. The Court denied the motion as to the '838 patent without prejudice, and a set a schedule for claim construction on March 31, 2011. Subsequently, the parties settled their claims related to the '838 and '253 as they relate to this litigation. However, the status of the '564 patent still remained in dispute with Defendants asserting that the patent was invalid: first, because it was obvious; and second, due to Plaintiffs' alleged inequitable conduct. The parties then filed the present motions for summary judgment.

III. Findings of Fact

1. In contrast to the changes over the years to the Ethinyl Estradiol("EE") dose, the 21/7 regimen for monophasic combined oral contraceptives ("COCs") remained prevalent between the invention of the COC in the late 1950s and Bayer's YAZ invention in 1993. (Ex. 1, Expert Report of Dr. Sanfilippo 17 ("Sanfilippo Rep.").)[2]

2. Bayer's inventors conducted a clinical trial, Study AA51, to compare a low-dose 21-day OC preparation with a low-dose 23-day preparation. (Ex. 5, Study Report AA51, Sept. 28, 1994; Ex. 6, Declaration of Jürgen Spona 4, June 30, 1994 ("Spona Declaration").)

3. The inventors concluded that "[t]he superiority of the 23-day regimen in comparison to the 21-day regimen with regard to the suppression of ovarian activity was shown in this study." (Ex. 5, Study Report AA51 at 3.)

4. The researchers who conducted the Missed Pill Study found that even when subjects missed pills, the women taking the 24-day regimen were still three times more likely to have less

2. Citations refer to exhibits attached to the declaration of Sundeep K. Addy, Doc. No. 255-3 (Exhibits at Doc. No. 255- 4, *et. seq.*).

ovarian activity compared to the 21-day group. (*See* Ex. 18, Klipping 2008 at 20; Ex. 15, Study Report A25848 at 4.)

5. The Guillebaud article taught the skilled person that a "shortened" PFI of 4-5 days may be suitable for a subgroup of women with certain special indications and should be utilized in conjunction with a "rather stronger combined pill, starting usually with one containing 50 µgs of ethinyloestradiol . . . ." (Ex. 24, Guillebaud 1987 at 43; Ex. 3, Carr Dep. 116:13-117:21.)

6. Dr. Guillebaud also taught the skilled person that the PFI could be eliminated, either in the short-term (for example, when a woman wishes to avoid the withdrawal bleed while on holiday) or more long-term (by administering three or four 21-day packs consecutively followed by a one week break). (Ex. 24, Guillebaud 1987 at 42-43.)

7. Based on his review of the prior art, Dr. Guillebaud emphasized that "the current PFI of seven (or six) days is acceptable for the majority of pill takers . . . ." (*Id.* 39 (emphasis added).)

8. The Guillebaud article unambiguously concluded that the 21/7 regimen was superior to the alternatives: "the strong suggestion that the pill-free interval may have health benefits—not only by reducing the total dose of artificial steroid per year but also by the regular break from the systemic actions—makes it probable that we should continue to use the current regimens for the majority of our patients." (*Id.* 43.)

9. The European Patent Office agreed with Bayer (and Dr. Carr's deposition admission), and concluded that the Guillebaud article teaches away from Bayer's claimed invention because it suggests use of a higher EE dose together with any shortened PFI, and encourages the skilled person to use regimens other than 24/4. (Ex. 28, Translation of Interlocutory Decision, June 15, 2009 ("[T]he alleged disclosure of a duration of 24 days followed by 4 days of placebo . . . in [Guillebaud 1987] is made in the context of a higher ethinylestradiol dosage and only for women with an increased frequency of break-through ovulations."); Ex. 29, Citation Sheet.)

10. The progestin doses disclosed in EP '607 are lower than the doses used in general purpose oral contraceptives on the market. (Ex. 1, Sanfilippo Rep. 45.)

11. EP '607 does not contain any teaching that the monthly regimen is provided to improve contraceptive efficacy; instead the skilled person would understand that the extended regimen was included because an effective hormone replacement therapy for premenopausal women requires a relatively constant supply of hormones to supplement their waning natural hormone production and treat their climacteric symptoms. (Ex. 1, Sanfilippo Rep. 47.)

12. The AU '094 application statement that DRSP can be used "analogously" with the EP '607 method only teaches the skilled person that DRSP can replace the non-DRSP progestins listed in EP '607 for premenopausal women in need of hormone replacement therapy ("HRT"). (Ex. 23, AU '094 5:3-5; Ex. 1, Sanfilippo Rep. 42.)

13. Molloy did not report any efficacy data for a 23-day regimen, nor suggest use of very low-dose pills, such as those containing 20 µg of EE. (*Id*. 49-50.)

14. Persons of skill in the art wrote contemporaneous letters (which were published and qualify as prior art) that did reject – and therefore teach away from – Molloy's evidence-free recommendation to use a 23/5 regimen with COCs containing 30 to 40 µg EE. (Exs. 30-32.)

15. There are no prior art references specifically teaching use of a 24/4 regimen for a COC containing 20 µg EE. (*See* Ex. 21, Carr Rep. *passim*.)

16. AA51 had unexpected and surprising results. (*See Supra* at 5-6, Ex. 6, Spona Declaration 4; Ex. 8, '564 patent 4:62-5:2.)

17. The Missed Pill Study shows the inventors were correct that the surprising superiority of the claimed 24/4 regimen applies to DRSP. The surprising increased efficacy of the 24/4 regimen using DRSP in a missed pill scenario would have been unexpected in 1993. (Ex. 1, Sanfilippo Rep. 58.)

18. According to the Dinger article, women taking DRSP/EE in a 24-day regimen (YAZ) had lower contraceptive failure rates at the end of each year in comparison to (1) women taking DRSP/EE in a 21-day regimen (Yasmin®); and (2) women taking any other OCs. (Ex. 39, Dinger 2011 at 37.)

19. FDA and European experts expressed doubts over whether the 24-day regimen would result in better contraceptive efficacy, and they were also skeptical of the safety profile in light of the increased monthly dose compared to Yasmin (which contains DRSP and 30 μg EE in a 21/7 regimen). (Ex. 1, Sanfilippo Rep. 71-75.)

20. Although initially met with skepticism, Bayer's invention was eventually widely praised by experts in the COC field. (*Id.* 75-79.)

21. Watson and Sandoz have copied Bayer's invention in an effort to seek FDA approval for their generic product prior to the expiration of Bayer's patent. (Ex. 50, Sandoz0000292; Ex. 51, WAT0000017.)

Background On Combined Oral Contraceptives

22. "Combined" oral contraceptives ("COCs"), combine two synthetic hormones: a synthetic estrogen and a progestogen, or progestin. (Ex. 1, Expert Report of Dr. Sanfilippo 7 ("Sanfilippo Rep.").)

23. Synthetic hormones mimic the way natural estrogen and progesterone work in a woman's body. (*Id.*)

24. A woman taking a COC releases no new eggs because her body is "tricked" into believing she is already pregnant. (*Id.*)

25. Until recently, COCs were administered to patients in a 21/7 regimen, meaning that the patient takes 21 days of pills with active ingredients (*i.e.*, the progestin/estrogen combination) followed by 7 inert, or "placebo" pills, that do not contain hormones. (*Id.* 17.)

26. In contrast, YAZ uses a 24/4 regimen (24 days of hormone-containing pills followed by 4 placebo pills). (Ex. 2, YAZ Physician Labeling.)

27. The estrogen component in a COC aids in the prevention of pregnancy. For example, synthetic estrogen assists with cycle control, meaning it reduces vaginal bleeding or spotting outside of the scheduled withdrawal bleed. (Ex. 1, Sanfilippo Rep. 7-8.)

28. Poor cycle control increases the likelihood that a woman will use COCs inconsistently and miss pills and also may cause a woman to discontinue COC use altogether. (*Id.*) Ethinyl Estradiol ("EE") also helps to inhibit the follicle stimulating hormone (FSH) that a woman's body naturally produces and increases the effectiveness of oral contraceptives by reducing the likelihood of ovulation. (*Id.*)

29. However, EE is also thought to be the main source for adverse side effects associated with oral contraceptives, including cardiovascular events, nausea, bloating, and breast tenseness or discomfort. (*Id.*)

30. For safety reasons, one of the main goals since the introduction of COCs has been to lower the dose of EE. (*Id.* 9.)

31. The first COCs contained high doses of EE (100-150 µg). (*Id.*)

32. During the 1970s, the EE dose declined to 50 µg, then 35 and 30 µg. (*Id.*)

33. Very low-dose COCs followed – these contained 20 µg of EE, and later 15 µg of EE. (*Id.*)

34. The first 20 µg EE pill approved for use in the United States was Loestrin® 21 1/20, approved in 1976. (*Id.* 10.) Another example of a 20 µg EE pill is Mercilon. (Ex. 3, Deposition of B. Carr 41:18-23, Mar. 14, 2011 ("Carr Dep."); Ex. 1, Sanfilippo Rep. 9.)

35. At the time of Bayer's invention in December 1993, Mercilon and Loestrin 21 were the exception, and nearly all monophasic COCs on the market contained 30 µg EE or more. (Ex. 1, Sanfilippo Rep. 9.)

Bayer's Development Of The 24-Day Regimen

36. In contrast to the changes over the years to the EE dose, the 21/7 regimen for monophasic COCs remained prevalent between the invention of the COC in the late 1950s and Bayer's YAZ invention in 1993. (*Id.* 17.)

37. Notably, the 21/7 regimen remained the standard even for several years after Bayer invented the 24-day regimen in 1993. (*Id.*)

38. When Drs. Pincus and Rock first invented the COC more than 50 years ago, they concluded that women would only accept this new method of birth control if it mimicked a woman's natural menstrual cycle with a monthly bleeding period triggered by a 7-day break from the active hormone ingredients. (Ex. 1, Sanfilippo Rep. 17; Ex. 3, Carr Dep. 63:23-64:5.)

39. Drs. Pincus and Rock discovered that a rapid decline in artificial hormones occurs during the 7-day hormone-free interval and results in a "withdrawal bleed." (Ex. 1, Sanfilippo Rep. 17.) This withdrawal bleed resembles the menstrual period and is often colloquially referred to as a "period" for simplicity. (*Id.* 17-18.)

40. These early pioneers believed that women would find the lack of a bleeding period disconcerting and would not use COCs. (Ex. 1, Sanfilippo Rep. 17.)

41. In addition to these various "acceptability" reasons, the original COCs also used the 21/7 because scientists believed that a 7-day pill-free interval ("PFI") could reduce potentially dangerous side effects that may result from more than 21-days of hormone-containing pills. (*Id.* 17-18.)

42. Much of the literature published before Bayer's invention in 1993 stressed the importance and superiority of the 7-day PFI and the monthly "rest" that it provided from synthetic hormones. (*See, e.g.*, Ex. 4, Excerpt from *Contraception: Science and Practice*, 78-79 (emphasis added).)

43. Bayer's inventors conducted a clinical trial, Study AA51, to compare a low-dose 21-day OC preparation with a low-dose 23-day preparation. (Ex. 5, Study Report AA51, Sept. 28, 1994.; Ex. 6, Declaration of Jürgen Spona 4, June 30, 1994 ("Spona Declaration").)

44. Each of the study subjects took three active treatment cycles of COCs with 75 µg of the progestin gestodene and 20 µg of EE. (Ex. 5, Study Report AA51 at 1-2.) Half of the subjects took pills using the 21/7 regimen while the others used the new 23/5 regimen. (*Id.* 2.)

45. The inventors monitored the size of "active follicle-like structures" to determine the extent of ovarian activity. (*Id.*)

46. The study established that the subjects in the 23-day group had significantly less ovarian activity than those in the 21-day group. (*Id.*)

47. The inventors concluded that "[t]he superiority of the 23-day regimen in comparison to the 21-day regimen with regard to the suppression of ovarian activity was shown in this study." (*Id.* 3.)

48. This surprising result was completely unforeseeable from the teaching of the prior art. (Ex. 6, Spona Declaration 4.)

Bayer's '564 Reissue Patent

49. Based on their pioneering work on the 23- and 24-day oral contraceptive regimens, Drs. Spona, Lüdicke, and Düsterberg ("the Bayer inventors") applied for a United States patent covering the 23- and 24-day regimen on June 30, 1994. (Ex. 9, Transmittal Letter for U.S. Patent App. No. 08/268,996, June 30, 1994.)

50. Pursuant to 35 U.S.C. § 119(a), U.S. Patent App. No. 08/268,996 claimed priority to an earlier-filed German patent application, which the inventors filed on December 22, 1993. (Ex. 9, Transmittal Letter for U.S. Patent App. No. 08/268,996). As a result, the application was entitled to claim the same effect in the United States as if it had been filed on December 22, 1993. *See* 35 U.S.C. § 119(a).

51. The USPTO granted U.S. Patent App. No. 08/268,998 on December 10, 1996. (Ex. 10, United States Patent No. 5,583,129 ("the '129 patent").)

52. Bayer later received a second patent on the 23- and 24-day regimen stemming from the same underlying application. (Ex. 11, United States Patent No. 5,824,667 ("the '667 patent").)

53. Both the '129 and '667 patents disclosed the results of Study Report AA51. (Ex. 10, '129 patent 4:20-50; Ex. 11, '667 patent 4:22-52.)

54. However, the patents contained a typographical error based on a misplaced decimal point in the drospirenone dosage range. (*See* Ex. 12, '564 Reissue Patent File History, Decl. of B. Düsterberg 4, Feb. 11, 2000.)

55. As provided for under standard PTO procedure, Bayer filed an application for a reissue patent to correct the inadvertent decimal-point error. (Ex. 13, '564 reissue application transmittal letter.)

56. This application resulted in the '564 patent, which is the asserted patent in this case. (Ex. 8, '564 patent.)

Bayer Applies Its Patented Invention To Develop YAZ

57. After the inventors' pioneering work resulting in the '564 patent, Bayer scientists conducted numerous additional clinical studies confirming the effectiveness of 23- and 24-day regimens. (Ex. 14, Excerpts from Study Reports AR62, AE24, AE23, A071, A09372, A11401, A12007, A21566, A07545, A25848, A25152, A25083, A29551, A30713.)

58. Bayer initially studied the gestodene/EE combination from Report AA51 in a 23-day regimen. (*Id.* (Reports AR62, AE24, AE23, A071).)

59. Eventually, Bayer studied a novel COC combining a new progestin, drospirenone DRSP), with 20 µg EE used in a 24/4 regimen. (*Id*. (Reports A09372, A11401, A12007, A21566, A07545, A25848, A25152, A25083, A29551, A30713).)

60. Study A25848 compared 21- and 24-day preparations of DRSP/EE COCs and studied the effect of each regimen on ovarian follicular development. (Ex. 15, Study Report A25848, May 6, 2005.)

61. Each subject was given pills containing 3 mg of DRSP in combination with 20 µg of EE over three active treatment cycles, with roughly half of the subjects using the 24-day regimen, while the remainder used the traditional 21-day regimen. (*Id.* 4, 21.)

62. In addition, Study A25848 introduced "intentional dosing errors" during the start of the third active cycle of treatment in both study groups. (*Id.* 1-2.)

63. Each subject omitted pills on days 1 to 3 of the third active cycle. (*Id.* 1.)

64. The purpose of the intentional dosing errors was to "mimic real life situations of women forgetting the intake of some pills." (Ex. 16, Deposition of J. Marr 46:16-24 (Feb. 19, 2010) ("2010 Marr Dep.").)

65. Dr. Marr explained his deposition that "This is also according to the available literature reflecting what happens in real life, that women miss to start the next blister pack for several reasons, because they don't remember that they have to start on the respective day, or because they don't have a prescription ready to get the next blister pack, or simply because [they] don't have the next blister pack at hand when they are supposed to start." (Ex. 17, Deposition of J. Marr 218:12-20 (May 14, 2009) ("2009 Marr Dep.").)

66. Study A25848 became known throughout the industry as the "Missed Pill Study." (*Id.* 230:2.)

67. Bayer published the results of the Missed Pill Study in a peer-reviewed article that disclosed two important findings about the drospirenone-containing 24-day regimen. (Ex. 18, Klipping 2008.)

68. The Missed Pill Study confirmed "that increasing the duration of active hormone intake to 24 days and shortening the hormone-free interval to 4 days with the [DRSP] 3 mg/EE 20 µg combined oral contraceptive results in greater suppression of ovarian activity compared with the conventional 21/7 regimen." (Ex. 18, Klipping 2008 at 22; *see also* Ex. 16, 2010 Marr Dep. 54:22-55:13.)

69. Notably, the researchers also founded that even when subjects missed pills the women taking the 24-day regimen were still **three times more likely** to have less ovarian activity compared to the 21-day group. (*See* Ex. 18, Klipping 2008 at 20; Ex. 15, Study Report A25848 at 4.) This finding is important because lower ovarian activity results in fewer inadvertent pregnancies.

70. Based on this and other data, Bayer sought approval from the FDA to market YAZ, Bayer's patented 24-day oral contraceptive containing 3 mg of DRSP in combination with 20 µg of EE. (Ex. 19, New Drug Application Cover Letter from N. Velez to D. Shames, Oct. 16, 2003.)

71. The FDA approved YAZ on March 16, 2006, and it quickly became one of the best-selling COCs in the United States. (Ex. 20, YAZ Approval Letter, Mar. 16, 2006.)

Level Of Ordinary Skill In The Art

72. The hypothetical person having ordinary skill in the art is a medical scientist involved in the research and development of oral contraceptives and having a Ph.D. degree in biological science or a person with a medical degree (e.g., an M.D. or a D.O.) and either several years of clinical experience administering combined oral contraceptives and/or having experience in the research and development of oral contraceptives. (Ex. 21, Carr Rep. 10; Ex. 1, Sanfilippo Rep. 6.)

The Prior Art

A. The Guillebaud Article

73. The Guillebaud article, entitled "The forgotten pill—and the paramount importance of the pill-free week," was published in the January 1987 edition of the *British Journal of Family Planning*. (Ex. 24, Guillebaud 1987.)

74. Dr. Guillebaud explained that when the 7-day pill-free interval (PFI) is lengthened from missed pills at the beginning or end of the monthly cycle, efficacy risks may arise in a subgroup of women who have certain specific conditions. (*Id.* 35-36.)

75. Dr. Guillebaud explained that for such women, "levels of oestradiol achieved suggest that a surge of LH [(luteinizing hormone)] might well be induced if the PFI were lengthened. Moreover, the ultrasound studies imply that in some cases a sufficiently ripe ovarian follicle would be present for fertile ovulation to result." (*Id.* 39.)

76. Dr. Guillebaud concluded that in this subgroup of women 7 pill-free days might be the maximum number of days that can elapse before ovulation might occur. (*Id.* 36.)

77. The special indications for shortening the pill-free interval arise when one of three "unique issues" are present: (1) a woman had a previous inadvertent conception while using an OC, particularly if there have not been any missed pills; (2) a woman with epilepsy that is being treated

with long-term enzyme-inducing drugs; or (3) a woman has difficulty absorbing exogenous (or external) hormones. (*Id.* 43.)

78. But when such circumstances are present, the Guillebaud article taught the skilled person that the "shortened" PFI of 4-5 days should be utilized in conjunction with a "rather stronger combined pill, starting usually with one containing 50 µgs of ethinyloestradiol . . . ." (*Id.*; Ex. 3, Carr Dep. 116:13-117:21.)

79. The Guillebaud article as a whole unmistakably teaches away from Bayer's claimed invention in at least three important respects. (Ex. 1, Sanfilippo Rep. 23-27.)

80. First, the article clearly states that the 21/7 (or a 22/6) regimen is the preferred COC regimen. (*Id.*)

81. Second, the article specifically teaches that in the limited situations where a 24-day regimen is useful, it should only be used in combination with a stronger dose of estrogen, starting at 50 µg of EE. (*Id.*)

82. Third, the article teaches that the preferred alternative to the traditional 21/7 regimen if one is employed is the elimination of the PFI entirely. (*Id.*) In contrast, Bayer's invention requires a 23/5 or 24/4 regimen with a very low-dose of 20 µg EE. (Ex. 8, '564 patent claims 13, 15.)

83. The Guillebaud article repeatedly teaches that the 21/7 regimen is the preferred regimen for the majority of pill takers. (Ex. 24, Guillebaud 1987 at 39, 43.)

84. Guillebaud cites a number of "definite advantages" to the traditional 7-day PFI, such as the monthly withdrawal bleed and the lower annual steroid quantity, reflecting the conventional wisdom of those skilled in the art. (*Id.* 42; Ex. 1, Sanfilippo Rep. 24.)

85. And even in those situations in which a 7-day pill-free interval is not ideal, Guillebaud's first and primary suggestion to the skilled person is to eliminate the pill-free interval, not shorten it. (Ex. 24, Guillebaud 1987 42-43.)

86. Guillebaud's limited suggestion of a shortened PFI is suggested only in combination with a higher-dose of EE. (Id. 43; Ex. 3, Carr Dep. 116:13-117:21.)

The EP '607 Patent Application

87. The EP '607 application is a European Patent Application published on January 20, 1988, entitled "Combination dosage form for premenopausal women." (Ex. 22, EP '607 at 1.)

88. Unlike Bayer's '564 patent (which does not claim hormone replacement therapy), EP '607 discloses a method of providing both hormone replacement therapy and contraception for women in "pre-menopause." (*Id.* 1:1-3.)

89. EP '607 defines "pre-menopause" as "the time around 40 years of age when a woman can reasonably be said to be approaching menopause (the last menstrual period) or the time when a woman feels the approach of menopause by experiencing pre-menstrual irregularities in her menstrual cycle or other hypoestrogenic symptoms." (*Id.* 1:17-23.)

90. The EP '607 application states that such women present special medical needs distinct from the general population of women: "The woman over forty is in a transitional period in which her hormone levels are waning; she still ovulates and yet she experiences many of the symptoms of the hypoestrogenic woman, insomnia, hot flushes, irritability, etc." (*Id.* 1:24-28.)

91. Thus, the invention disclosed in the EP '607 application is for older women who need hormone replacement therapy to treat pre-menopausal symptoms. (Ex. 1, Sanfilippo Rep. 42.) Because these women also ovulate, pre-menopausal women also need contraception. (Ex. 22, EP '607 2:21-22.)

92. The EP '607 application proposed a preparation containing a low-dose estrogen, together with a very low-dose progestin. (Ex. 22, EP '607 1:6-7.)

93. The progestin doses disclosed in EP '607 are lower than the doses used in general purpose oral contraceptives on the market. (Ex. 1, Sanfilippo Rep. 45.)

94. EP '607 assumed that such very low-dose preparations would be effective for contraception. (Ex. 22, EP '607 2:15-31.)

95. Further, the EP '607 pills are administered for 23-26 days followed by a corresponding 2-5 day hormone-free-interval, for a total of 28 days in the administration cycle. (*Id.* 1:10-14.)

96. The prior art COC dose for the progestin levonorgestrel is 0.125 to 0.250 mg per day. (*Id.* 46.)

97. The prior art COC dose for the progestin gestodene is 0.075 mg per day. (*Id*.)

98. The prior art COC dose for the progestin desogestrel is 0.025 to 0.100 mg per day. (*Id.*)

99. The prior art COC dose for the progestin norethindrone is 0.500 to 1.0 mg per day. (*Id.*)

100. As of 1993 the prior art taught that 2.0 mg DRSP was an effective ovulation inhibition dose for "normal women." (Ex. 28, Oelkers 1991 at 837.)

The AU '094 Patent Application

101. The AU '094 application is an Australian Patent Application published on November 22, 1990, entitled, "Dihydrospirorenone as an antiandrogen." (Ex. 23, AU '094.)

102. AU '094 is the Australian counterpart to Bayer's United States Patent No. 5,569,652 ("the '652 patent"), which the inventors disclosed to the USPTO during the prosecution of the '564 reissue application. (Ex. 8, '564 Patent IDS.)

103. Like EP '607, AU '094 is primarily directed to premenopausal women and the unique hormonal needs of such women. (Ex. 23, AU '094 2:24-30.) AU '094 also noted that premenopausal women can suffer from androgenic disorders. (*Id.* 2:31-3:3.)

104. To address the aforementioned problems, the AU '094 application discloses the use of drospirenone (DRSP) in a broad range of doses. (*Id*. ("the dose of [drospirenone] can be 0.5 to 50 mg per day, preferably 1-10 mg per day for all uses of this invention.")

105. AU '094 taught the skilled person that DRSP has anti-androgenic properties (*Id.* 3:8-17), and noted that DRSP also has a gestagenic effect (meaning it can be used to achieve contraception), and an anti-aldosterone effect. (*Id*. 1a:6-2:4.)

106. Based on these properties, AU '094 taught the skilled person that DRSP could be used "analogously" to the methods in EP '607 for premenopausal women who need simultaneous hormone replacement therapy and contraception. (*Id.* 5:24-27; Ex. 1, Sanfilippo Rep. 46).)

107. The AU '094 application statement that DRSP can be used "analogously" with the EP '607 method only teaches the skilled person that DRSP can replace the non-DRSP progestins listed in EP '607 for premenopausal women in need of hormone replacement therapy ("HRT"). (Ex. 23, AU '094 5:3-5; Ex. 1, Sanfilippo Rep. 42.)

108. Notably, most HRT's are administered once-daily, thus there is no comparable history and tradition of 21/7 HRT's as with COCs. (Ex. 1, Sanfilippo Rep. 47.)

109. As a result, there is no teaching or even suggestion to skilled persons in either AU '094 or EP '607 that they should deviate from over three decades of the 21/7 regimen when developing a general purpose COC that is not intended for premenopausal women who need simultaneous HRT. (*Id*.) The combination of the two references simply contain no teaching that would lead the skilled person to use a 24/4 regimen outside the limited context of premenopausal women who need HRT. (*Id*.)

The Molloy Letter to the Editor

110. "'Missed pill' conception: fact or fiction?" is a short letter to the editor in the *British Medical Journal*, published on May 18, 1985. (Ex. 25, Molloy 1985.)

111. Dr. Molloy reported the results of a small study of ovarian follicular growth in 19 women taking various oral contraceptives. (*Id.* 1474.)

112. Specifically, the study measured the size of ovarian follicles observed in each subject at day 21 (the last day of active treatment), day 28 (the end of the pill-free-interval), and day 7 (the seventh day of the following pill-taking cycle). (*Id.*)

113. Notably, none of the subjects were taking a COC with 20 µg EE, as required in Bayer's asserted claims. (*See* Ex. 1, Sanfilippo Rep. 32.)

114. All of the COCs in the Molloy letter contained doses of EE, between 30 and 40 µg. (*Id.*)

115. Further, the subjects in the Molloy letter took COCs in a 21/7 regimen. (*Id.* 32-33, 49-50.)

116. Dr. Molloy reported that he did not detect any ovarian follicles in most subjects on day 21 of the first cycle or day 7 of the following cycle. (Ex. 25, Molloy 1985 at 1475.)

117. And even on the last day of the pill-free interval, Molloy only observed very small ovarian follicles that varied in diameter between 3 and 10 mm on the last day of the pill-free interval. (*Id.*)

118. However, the skilled person understood at the time that follicles with diameters between 3-10 mm are negligible in terms of ovulation – equivalent to a near-zero chance of ovulation. (Ex. 16, 2010 Marr Dep. 82:18-83:13.)

119. The Molloy letter addresses a non-existent problem because it reports the existence of *de minimis* ovarian follicles (ranging from 3-10 mm in diameter) after the 7-day PFI. (Ex. 25, Molloy 1985 at 1475.)

120. Dr. Molloy concluded with the suggestion of a 23/5 or 21/7 regimen of COCs containing 30 to 40 µg EE to prevent such small follicle growth. (Ex. 25, Molloy 1985 at 1474.)

121. Molloy did not report any efficacy data for a 23-day regimen, nor suggest use of very low-dose pills, such as those containing 20 µg of EE. (Ex. 1, Sanfilippo Rep. 49-50.)

122. Molloy did not report endogenous hormone levels, and absent such data the skilled person understood that such small follicles by themselves pose no realistic possibility of ovulation. (Ex. 16, 2010 Marr Dep. 82:18-83:13.)

123. Reliable determinations of active follicles require additional measurements of endogenous hormones such as estradiol, progesterone, luteinizing hormone (LH) or follicle-stimulating hormone (FSH) – none of which Molloy measured or described. (Ex. 25, Molloy 1985 at 1475.)

124. Based on small follicle size alone Molloy made the unsupported suggestion that women taking a COC containing 30-40 µg EE could use a 23/5 regimen to reduce the risk of missed-pill conception. (Ex. 25, Molloy 1985 at 1475.)

125. Moreover, the Molloy reference presented no data demonstrating that the observed follicles would be meaningfully reduced with only two additional days of pill-taking. (Ex. 1, Sanfilippo Rep. 33.)

126. Such a head-to-head comparison of the regimens would have been necessary for the skilled person to make any judgments as to whether any reduction in follicle size from a 23-day regimen would be meaningful compared to a 21-day regimen. (Ex. 3, Carr Dep. 157:20-25.)

Prior Art Related To 20 µg EE COC pills

127. By the time of Bayer's invention in December 1993, the skilled person understood that 21/7 regimen COCs were largely "fail safe" – and further understood that the previous problems with the original 21/7 low-dose 20 µg EE COCs (Loestrin 21 1/20, introduced in the 1970s) had been overcome with a new low-dose COC called Mercilon. (Ex. 1, Sanfilippo Rep. 9-17.)

128. Mercilon combined a new progestin (desogrestrel) with 20 µg EE, using the standard 21/7 regimen. (*Id.*)

129. The prior art taught the skilled person that – unlike earlier 20 µg EE COCs – Mercilon achieved contraceptive efficacy and cycle control akin to COCs containing 30 µg EE even when women missed pills. (*Id.*, citing Ex. 33, Fiorettie 1987 Article; Ex. 34, Bilotta 1989 Article; Ex. 35, Kuhl 1992 Article; Ex. 36, Fotherby 1992 Article; Ex. 37, Akerlund 1993.)

130. There are no prior art references specifically teaching use of a 24/4 regimen for a COC containing 20 µg EE. (*See* Ex. 21, Carr Rep. *passim*.)

Objective Evidence Of Non-Obviousness

Unexpected Results Of The Claimed Invention

131. The unexpected results of Bayer's invention were first shown in Study Report AA51, the results of which were summarized in the '564 patent. (Ex. 5, Study Report AA51.)

132. AA51 had unexpected and surprising results. (*See Supra* at 5-6, Ex. 6, Spona Declaration 4; Ex. 8, '564 patent 4:62-5:2.)

133. Study AA51 showed a statistically significant difference in suppressed ovarian activity between the claimed regimen and the 21-day regimen. (Ex. 5, Study Report AA51 at 3.)

134. Study AA51's results were published in a peer-reviewed journal that experts cited repeatedly for 14 years without objecting to any of the "problems" Dr. Carr raises. (Ex. 1, Sanfilippo Rep. 55; Ex. 38, Spona 1996.)

135. The Missed Pill Study shows the inventors were correct that the surprising superiority of the claimed 24/4 regimen applies to DRSP. The surprising increased efficacy of the 24/4 regimen using DRSP in a missed pill scenario would have been unexpected in 1993. (Ex. 1, Sanfilippo Rep. 58.)

136. The International Active Surveillance of Women Taking Oral Contraceptives ("INAS") is an ongoing study of various COCs used in the United States and Europe. (Ex. 39, Dinger 2011.)

137. Although the INAS study is ongoing in both the United States and Europe, the Dinger article only analyzes the current data from subjects in the United States. (*Id.* 33.)

138. INAS is a study of the efficacy and safety of COCs as they are actually used under "real-world" conditions rather than a controlled clinical trial. (*Id.* 34.)

139. The Dinger article reports on the first three years of data from the U.S. cohort of study subjects and 99,382 patient years of data. (*Id.* 35.)

140. According to the Dinger article, women taking DRSP/EE in a 24-day regimen (YAZ) had lower contraceptive failure rates at the end of each year in comparison to (1) women taking DRSP/EE in a 21-day regimen (Yasmin®); and (2) women taking any other OCs. (*Id.* 37.)

141. Unlike AA51 and the Missed Pill Study, which were conducted in closely-monitored clinical settings with detailed protocols to ensure compliance with pill-taking in a much smaller group of subjects over just three treatment cycles, INAS reports the surprising real-world efficacy and safety of Bayer's claimed invention in an extremely large group of subjects (over 50,000 women) studied over a much longer period of time (3 years of data to date). (Ex. 39, Dinger 2011 at 34-35; Ex. 1, Sanfilippo Rep. 58-68.)

Expert Skepticism Of The Invention

142. FDA experts expressed doubts over whether the 24-day regimen would result in better contraceptive efficacy, and they were also skeptical of the safety profile in light of the increased monthly dose compared to Yasmin (which contains DRSP and 30 μg EE in a 21/7 regimen). (Ex. 1, Sanfilippo Rep. 71-75.)

143. The FDA informed Bayer that the application could only be approved if Bayer provided additional data "demonstrat[ing] a clinical benefit for the 24-day regimen over that provided by a 21-day regimen to offset the increased potential risk associated with the additional 3 days of [DRSP/EE]." (Ex. 40, 11/17/04 Griebel Letter.)

144. Alternatively, the FDA suggested that Bayer propose a 21-day regimen, which shows that the conventional wisdom of 21/7 superiority continued. (*Id.*)

145. Bayer's invention likewise faced skepticism from European regulators regarding YAZ's benefits and safety compared to Bayer's Yasminelle® product, which has the same ingredients and doses as YAZ but is administered in a 21/7 regimen. (Ex. 41, 2/28/08 Submission of Consolidated Written Response; Ex. 42, 1/29/08 Submission of Consolidated Day 60 Response Dossier.)

Industry Praise For The Invention

146. Although initially met with skepticism, Bayer's invention was eventually widely praised by experts in the COC field. (Ex. 1, Sanfilippo Rep. 75-79.)

147. For example, several articles have recognized the *Contraception* article reporting the results of Study AA51 as the first peer-reviewed publication reporting the surprising degree of ovarian suppression from a slightly extended pill-taking regimen. (*Id*. (citing Exs. 43-48).)

148. Even as late as 1999 experts in the field described the 24/4 regimen as an "innovative strategy." (Ex. 49, Sullivan 1999.)

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Copying Of The Invention

149. Watson and Sandoz have copied Bayer's invention in an effort to seek FDA approval for their generic product prior to the expiration of Bayer's patent. (Ex. 50, Sandoz0000292; Ex. 51, WAT0000017.) Additionally, manufacturers TEVA and LUPIN have copied Bayer's invention in order to market a generic product.

IV. Analysis

"Because patents are presumed valid, a moving party seeking to invalidate a patent at summary judgment must submit such clear and convincing evidence of facts underlying invalidity that no reasonable jury could find otherwise." TriMed, Inc. v. Stryker Corp., 608 F.3d 1333, 1340 (Fed. Cir. 2010); Microsoft Corp. v. i4i Ltd. P'ship, 131 S. Ct. 2238, 2246 (2011). Obviousness is a question of law with underlying factual issues. See KSR Int'l Co. v. Teleflex Inc., 550 U.S. 398, 427 (2007). A patent shall not issue "if the differences between the subject matter sought to be patented and the prior art are such that the subject matter would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains." 35 U.S.C. § 103(a); KSR, 550 U.S. at 406-407. What a particular reference discloses is a question of fact, as is the question of whether there was a reason to combine certain references. See McGinley v. Franklin Sports, Inc., 262 F.3d 1339, 1352 (Fed. Cir. 2001); Para-Ordnance Mfg., Inc. v. SGS Imps. Int'l, Inc., 73 F.3d 1085, 1088 (Fed. Cir. 1995). Under the four-part test for obviousness detailed in Graham v. John Deere Co. of Kansas City, 383 U.S. 1, 17-18 (1966), the court must consider (1) the scope and content of the prior art; (2) the difference between the prior art and the claimed invention; (3) the level of ordinary skill in the art; and (4) any objective evidence of nonobviousness. See also, Transocean Offshore Deepwater Drilling, Inc. v. Maersk Contractors USA, Inc., 617 F.3d 1296,1303 (Fed. Cir. 2010).[3] The objective evidence of nonobviousness relevant in this action includes

[3] The level of ordinary skill in the art has been agreed to by all parties. Each parties' expert used the same description and qualifications to describe the level of ordinary skill in the art in 1993. Therefore, this issue is not in dispute in this litigation.

unexpected results of the claimed invention, expert skepticism, industry praise for the invention, and copying. See id. Objective evidence "must always be considered when available." Constant v. Advanced Mircro-Devices, Inc., 848 F.2d 1560, 1572 (Fed. Cir. 1988).

"[I]nventions in most, if not all, instances rely upon building blocks long since uncovered, and claimed discoveries almost of necessity will be combinations of what, in some sense, is already known." KSR, 550 U.S. at 418-19. As a result, an invention "composed of several elements is not proved obvious merely by demonstrating that each of its elements was, independently, known in the prior art." Id. at 418. Instead, "it can be important to identify a reason that would have prompted a person of ordinary skill in the relevant field to combine the elements in the way the claimed new invention does." Id. "When prior art references require selective combination by the court to render obvious a subsequent invention, there must be some reason for the combination other than the hindsight gleaned from the invention itself." Uniroyal, Inc. v. Rudkin-Wiley Corp., 837 F.2d 1044, 1051 (Fed. Cir. 1988).

Individual prior art references must not be viewed in isolation from the context of the teachings in the prior art as a whole, so that the teachings of the prior art taken together can supersede the teachings of any individual reference if they conflict. See Standard Mfg. Co. v. United States, 25 Cl. Ct. 1, 53 (Cl. Ct. 1991)(each patent, including each prior art reference, must be considered as a whole); Uniroyal, 837 F.2d at 1051 (something in the prior art as a whole must suggest the desirability and thus the obviousness of making the combination).

Courts assessing obviousness must be cautious of "distortion caused by hindsight bias" and of "arguments reliant upon *ex post* reasoning." KSR, 550 U.S. at 421.

> In retrospect, [the inventor's] pathway to the invention, of course, seems to follow the logical steps to produce these properties, but at the time of invention, the inventor's insights, willingness to confront and overcome obstacles, and yes, even serendipity, cannot be discounted.

Ortho-McNeil Pharm., Inc. v. Mylan Labs., Inc., 520 F.3d 1358, 1364 (Fed. Cir. 2008).

Defendants contend that clear and convincing evidence establishes that Plaintiffs' patent is invalid for obviousness for the following reasons: (1) the claimed combination of drospirenone and EE for oral contraception, at the claimed doses, was *per se* conventional on December 22, 1993; (2) the 23/5 or 24/4 dosing regimen claimed in the Spona patent was expressly taught by prior art references; and (3) there was a clear motivation to combine the teachings of the cited prior art to arrive at the subject matter claimed in the Spona patents, i.e., the prior art recognized the problem and taught the solution. However, the Court disagrees and finds that Defendants have not met their burden in demonstrating clear and convincing evidence showing that the '534 patent is invalid as obvious.

A. Bayers' Claims are Not Obvious Because the Prior Art as a Whole Taught Away from Bayers' Claimed Invention

An invention is not obvious if the prior art "teaches away" from the invention. KSR, 550 U.S. at 416. If the facts establish that the prior art as a whole actually "teaches away" from the claimed invention, the person of ordinary skill in the art would not have been motivated to take the path the inventors took, and the claimed invention is not obvious. In re Hedges, 783 F.2d 1038, 1041 (Fed. Cir. 1986). An inventor's decision to proceed "contrary to the accepted wisdom of the prior art" is "strong evidence of nonobviousness." W.L. Gore & Assocs. v. Garlock, Inc., 721 F.2d 1540, 1552-53 (Fed. Cir. 1983). Prior art "teaches away" from the claimed invention if one skilled in the art "would be discouraged from following the path set out in the reference, or would be led in a direction divergent from the path that was taken by the [inventor]." In re Gurley, 27 F.3d 551, 553 (Fed. Cir. 1994).

Having extensively reviewed the prior art, the Court concludes that rather than establishing obviousness by clear and convincing evidence, the prior art clearly teaches away from the Spona Patent's 23/5 or 24/4 dosing regimen, except in very specific circumstances. For example, Defendants cite the 1987 Guillebaud article as evidence of obviousness, but the Guillebaud article teaches away from Bayers' claimed invention in three ways. First, the article clearly teaches that the

21/7 regimen for administering COCs is superior, highlighting the advantages arising from the seven-day Pill Free Interval ("PFI"). Guillebaud also teaches the skilled person that if deviation from the traditional regimen is necessary, the best solution is to eliminate the PFI entirely. Bayers' invention instead shortens the PFI. Finally, the article teaches that if the PFI is to be shortened in the case of women who are susceptible to "breakthrough ovulation," then the dose of EE should be correspondingly stronger, suggesting a starting dose of 50 µg. This suggestion teaches completely away from Bayers's invention which shortens the PFI, but maintains a low dose of EE. Finally, Guillebaud recommends the shortened PFI only in extreme cases: women susceptible to breakthrough ovulation, patients on long-term enzyme-inducing drugs, primarily those treated for epilepsy, and those suspected of malabsorption of exogenous hormones. None of these teachings suggests what Bayer did to shorten the PFI for most women with a lower dose of EE.

Defendants also cite the Molloy letter to the editor published in the *British Medical Journal* which suggested shortening the PFI to five days for COC's containing 30 to 40 µg EE in order to decrease the size or number of ovarian follicles. In response to Molloy's letter, three separate letters were written by scientists skilled in the art of oral contraception criticizing Molloy's data and suggestions to shorten the PFI. Primarily, the responses criticized Molloy for increasing exposure to artificial steroids. Included in those criticizing Molloy was Guillebaud.

Another reason Defendants assert that the invention was obvious was because the problem in need of a solution was "missed-pill pregnancies" which solution was known in the prior art. However, this argument is flawed because "missed-pill pregnancies" did not pose a meaningful problem in need of a solution. Guillebaud taught the skilled person that for the vast majority of women the pill was "fail-safe." Despite the fact that twenty-seven percent (27%) of women who took the pill in Gillebaud's study reported missing pills, pregnancy rarely resulted. This was the basis for Gillebaud's assertion that due to the "definite advantages" of the seven day PFI, a person with the ordinary skill in the art should use the 21/7 monthly regimen.

The Landgren 1991 prior art reference explicitly rejected Bayer's 23/5 regimen. Landgren studied the effect of missing three (3) pills at the beginning or end of the PFI thereby studying the effect of a ten (10) day PFI. Landgren concluded that though there was a risk of some restoration of ovarian activity during the lengthened PFI, there was not a meaningful risk of actual ovulation or inadvertent pregnancy. Landgren concluded that reducing the PFI to five days in low-dose COCs would result in negligible gains in "safety." Similarly, the Killick 1990 prior art taught skilled persons that an eleven (11) day PFI would not result in pill failure in most cases. In the eight prior art studies that examined PFI intervals longer than seven days, all concluded that the risk of missed-pill pregnancies was not meaningful.

Thus, the missed-pill prior art literature wholly rejects Defendants' assertion that there was a known missed-pill problem. The absence of a known missed-pill problem in the prior art is grounds for denying Defendants' motion because Defendants have not identified any other reason that the hypothetical skilled person would combine the various prior art references upon which Defendants rely. See Winner Int'l Royalty Corp. v. Wang, 202 F.3d 1340, 1349 (Fed. Cir. 2000)(holding that absent a problem to be solved the invention was not obvious because there was no reason for the skilled person to combine various prior art references into the claimed invention).

B. Bayers' Claims are Not Obvious because Prior Art Concerning 21/7 COCs containing 20 µgs EE Taught Away from Bayer's Claimed Invention

The prior art related to 21/7 COCs containing 20 µgs of EE further establishes that the prior art as a whole taught the skilled person that there was no need to develop a new regimen for low-dose COCs. The first low-dose COC containing 20 µg of EE was approved by the FDA in 1976. Loestrin 21 contains 20 µg EE. Mercilon became the second COC containing 20 µg of EE approximately ten years later. Mercilon, however used a different progestin called desogestrel. The prior art taught that Mercilon and Loestrin achieved contraceptive efficacy comparable to high dose COCs containing a higher EE dose even when women missed pills. The prior art unanimously praised the contraceptive efficacy of Mercilon, even in missed-pill situations. Thus, the hypothetical skilled person in 1993

knew that there were two low-dose COCs on the market using the 21/7 monthly regimen. Both products had been widely studied and approved as safe and effective for the prevention of pregnancy. This widespread acknowledgment of the efficacy of Loestrin and Mercilon taught away from the claimed invention and removed motivation to develop a different regimen for COCs containing 20 µg of EE. Given the perceived superiority of the 21/7 regimen, the strong belief in the efficacy of 20 µg EE COCs and the dose-dependent adverse EE side effects, the hypothetical person of ordinary skill would have concluded in 1993 that any benefit of a 24/4 or 23/5 regimen would be negligible and would not justify exposing women to a higher monthly dose of synthetic hormones. In fact, the actual skilled persons in the art in 1993 came to that conclusion. See (Ex. 11, Landgren 1991; Ex. 5, Bye 1985; Ex. 6 Tayob & Guillebaud 1985; Ex. 7, Killick 1985).

C. Defendant's Proposed Combination of Prior Art References does not Establish that Bayer's Invention was Obvious in 1993

Defendants' motion improperly analyzes individual claim elements in isolation rather than the claimed invention as a whole. Defendants contend that the claimed 23- and 24-day regimens are the only asserted novel aspect of Bayers' invention, because they assert the claimed dose ranges of drospierenone and EE were "*per se*" conventional in 1993. Defendants conclude that if the claimed monthly pill-taking regimen was known in 1993, the invention was obvious. However, "[t]he critical inquiry is whether there is something in the prior art as a whole to suggest the desirability, and the obviousness, of making the combination." Custom Accessories, Inc. v. Jeffrey-Allan Indus., Inc.. 807 F.2d 955, 959 (Fed. Cir. 1986)(internal quotations omitted).

The known range of effective doses of drospirenone and EE in 1993 were revealed in the context of the traditional 21/7 regimen. What was not known based on the prior art was the desirability of using the claimed drospirenone and EE doses together with the claimed monthly

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regimen. The inventor testimony relied upon by Defendants in support of their motion supports this assertion:

> The main advantage of this invention is that you could use a low dose oral contraceptive with a low dose per day which provides by extending the intake interval by two or three days, which provides a similar ovarian suppression than a higher dose one with, for instance, 30-microgram ethinylestradiol would provide . . . This was never demonstrated before. This was the absolutely first study to show that.

(Ex. 17, 5/19/09 Dusterberg Dep. 110:18-111:9).

Since the Court must analyze the claim as a whole, the Court can deny Defendants' motion for summary judgment and grant Plaintiffs' motion, because the clear and convincing evidence does not show that Bayer's invention was obvious.

D. The Prior Art did not teach the Skilled Person to Combine Defendants' Prior Art References Into Bayer's Claimed Invention as a Whole

Despite Defendants' attempts to parse Bayer's expert's testimony into "admissions" which they then rely on to demonstrate that the prior art showed that the claimed invention was obvious, a clear reading of Dr. Sanfilippo's entire report makes clear that Defendants have provided no evidence that a person of ordinary skill in the art would have thought it advisable to combine various clips from prior art references into Bayers' claimed invention. Instead, Dr. Sanfilippo's entire report makes it clear that a person of ordinary skill in the prior art would not have concluded that combination of the claims would have been advisable. While the cited references and snippets from Dr. Sanfilippo's expert report provide a hindsight roadmap to find obviousness, structuring the prior art in order to modify and reconstruct the invention is impermissible. See Interconnect Planning Corp. v. Feil, 774 F.2d 1132 (Fed. Cir. 1985)(the prior art references as a whole must be considered, in addition to examining the claims as a whole, so that their teachings are applied in the context of their significance to a person skilled in the art at the time of the invention); In re Shuman, 361 F.2d 1008, 1012 (C.C.P.A. 1966)("It is impermissible to first ascertain factually what appellants did and then view the prior art in such a manner as to select from the random facts of that art only those which may be

modified and then utilized to reconstruct [the patentees'] invention from such prior art."). Defendants' reliance on the Guillebaud article, the Molloy article, the Goldstruck article and the EP '607 patent application, and the AU '094 patent application impermissibly pick and choose from the prior art references without examining the prior art as a whole.

The Court has already demonstrated that the Guillebaud and Molloy articles taught away from the claimed invention. The Goldstruck 1987 article asserted that 28-day pill packs (containing 21 active pills and 7 placebos) were preferable to 21-day pill packs (containing 21 active pills and no placebos) because everyday pill taking reduces the overall risk of pill-taking errors. However, the Goldstruck article then cited Guillebaud's article's suggestion that certain women at risk of pill-failure should consider a 24-day high-dose EE pill regimen. However, the Court has already shown that Guillebaud's article taught away from the claimed invention. Bayer's invention must be contrasted from the Goldstruck and Guillebaud articles because the articles recommend high-dose EE pills with a shortened PFI whereas the invention relies upon a low-dose regimen.

Plaintiffs correctly contend that to support their position Defendants engage in a selective reading of the prior art as a whole and disregard the central teachings of the two patent references. The claimed pharmaceutical composition in both the EP '607 and the AU '094 patent applications were developed for women who have reached premenopause. The invention disclosed in the EP '607 patent is explicitly intended for use by older women who need hormone replacement therapy to treat premenopausal symptoms. The EP '607 application teaches a method for providing simultaneous oral contraception and hormone replacement therapy ("HRT") to premenopausal women by administering very low doses of a progestin together with an estrogen in a 23/5, 24/4, 25/3 or 26/2 regimen.[4]

4. Defendants assert that Dr. Sanfilippo admitted during his deposition that the EP '607 application disclosed the use of 24 active days of therapy followed by 4 pill-free days. However, Dr. Sanfilippo noted that any disclosure of the 24-day regimen in EP '607 was made only in the context of a specific "patient population" (premenopausal women) and for the dual purpose of HRT and oral contraception.

The EP '607 application does not teach the skilled person that a 23/5 or 24/4 monthly regimen would be desirable for women who do not need hormone replacement therapy. Instead, the skilled person would understand that the EP '607 application taught a 24/4 regimen because an effective HRT for premenopausal women requires a relatively constant supply of hormones to supplement waning endogenous hormone production and treat climacteric symptoms. (Ex. 2, Sanfilippo Rep. 47). There would have been no reason for a person skilled in the art to move away from the prior art's teachings as a whole that the 21/7 regimen was preferable and move to a regimen intended to provide HRT and oral contraception.

Even if skilled persons would have been motivated to use drospirenone with the 24/4 regimen, they would not create a composition using Bayer's claimed drospirenone dose between 2.5 to 3.0 mg. This is because the EP '607 application taught the desirability of very low progestin doses that were below the doses used in any oral contraceptive that had been approved for the prevention of pregnancy. As a result the skilled person following the very low-dose progestin teachings of EP '607 would select a drospirenone dose below Bayer's claimed 2.5 to 3.0 mg. Effectively, the very low-dose progestin teachings of the EP '607 application teaches away from Bayer's claimed drospirenone dose and cannot render claims 13 and 15 *prima facie* obvious. See McGinley, 262 F.3d at 1354; Gurley, 27 F.3d at 553.

Therefore, the Court must deny Defendants' motion and grant Plaintiffs', because Defendants have not produced clear and convincing evidence that it was obvious to create an oral contraceptive combining 3mg DRSP/20 µgs EE, with a 23/5 or 24/4 regimen. See Winner, 202 F.3d at 1349. In Winner, the Federal Circuit rejected an attempt to combine prior art references to establish obviousness based on facts similar to those present here. In Winner, the district court held that skilled persons would have had no reason to combine two prior art references because they did not perceive any meaningful problems with the long-used prior art method:

> [T]here was no apparent disadvantage to the dead-bolt mechanism of Johnson, and therefore the motivation to combine would not stem

> from the "nature of the problem" facing one of ordinary skill in the art, because no "problem" was perceived . . .

Id. at 1349. The Federal Circuit affirmed because the skilled person would not have combined prior art references if they did not think it would be desirable to tradeoff the benefit of security taught in one prior art reference, for the benefit of convenience taught in a second prior art reference. Id. The court explained that "[m]otivation to combine requires the [tradeoff to be desirable]." Id.

Winner's analysis applies to the facts here. The prior art taught the skilled person that there was no apparent disadvantage to using 20 μg EE pills in a 21/7 regimen because missed pills do not pose a meaningful pregnancy risk, and both Loestrin and Mercilon had proven safe and effective in both clinical trials and real-world use. The prior art also taught the skilled person that abandoning the 21/7 regimen in favor of a 24/4 regimen had disadvantages: a higher monthly and yearly dose of steroids, loss of the 7-day PFI's "definite advantages" (including the reversability of contraceptive effects and positive effects on HDL-cholesterol concentrations as noted in Guillebaud). Thus, as in Winner, the skilled person would have concluded that it was not desirable to combine the 20 μg EE prior art pills with the handful of unrelated prior art references to a 24/4 or 23/5 regimen.

E. Bayer's Substantial, Strong Objective Indicia of Non-obviousness

The Bayer Plaintiffs have presented strong objective evidence of non-obviousness for which Defendants have done little to controvert with specific, non-speculative evidence.

1. Unexpected Results of Claimed Invention

Evidence that the invention had "unexpected results" can rebut a prima facie case of obviousness if the "claimed invention exhibits some superior property or advantage that a person of ordinary skill in the art would have found surprising or unexpected." In re Soni, 54 F.3d 746, 750 (Fed. Cir. 1995). "[T]hat which would have been surprising to a person of ordinary skill in the relevant art would not have been obvious." In re Mayne, 104 F.3d 1339, 1343 (Fed. Cir. 1997).

The unexpected results of Bayer's invention were first shown in Study Report AA51, the results of which were summarized in the '564 patent. AA51 had unexpected and surprising

results. While Defendants assert that the study was not scientifically proper, objecting to "assay variability," statistical significance and serum estradiol measurements, the objections are not relevant or misstate the facts. Study AA51 showed a statistically significant difference in suppressed ovarian activity between the claimed regimen and the 21/7 regimen. The objections also ignore that AA51's results have been published in a peer-review journal and that results have been cited for fourteen (14) years without the objections made by Defendants' expert.

Defendants also object to the reports' failure to provide any information regarding the combination preparations claimed in the '564 reissue patent. However, a skilled person in the art would have known that the 23-day results using gestodene as the progestin are applicable to alternative progestins such as DSRP. The Missed Pill Study shows the inventors were correct that the surprising superiority of the claimed 24/4 regimen applies to DSRP. The surprising increased efficacy of the 24/4 regimen using DSRP in a missed pill scenario would have been unexpected in 1993. Evidence of unexpected results includes facts beyond what was known at the time of the invention and includes later-found properties of the invention that would have been unexpected at the time of the invention. See Knoll Pharm Co. v. Teva Pharms. USA, Inc., 367 F.3d 1381, 1385 (Fed. Cir. 2004).

Additionally, International Active Surveillance of Women Taking Oral Contraceptives ("INAS"), an ongoing study of various COCs used in the United States and Europe, provides compelling evidence of the contraceptive superiority of Bayer's claimed invention. INAS is a study of the efficacy and safety of COCs as they are actually used under "real-world" conditions rather than in controlled clinical trials. The Dinger article reports on the first three years of data from the U.S. group of study subjects and includes 99,382 patient years of data.

INAS shows that women taking DRSP/EE in a 24-day regimen (YAZ) had lower contraceptive failure rates at the end of each year in comparison to women taking DRSP/EE in a 21-day (Yasmin) regimen and in comparison to women taking any other COCs. INAS confirms the surprising result that Bayer's claimed 24/4 DRSP/20 μg EE COC provides significantly greater contraceptive efficacy even when compared to 30 μg EE COCs. But unlike Study AA51 and the

Missed Pill Study, which were conducted in closely-monitored clinical settings, INAS reports real-world efficacy and safety, and contains an extremely large group of subjects (50,000+) for a longer period of time, three (3) years.

Thus, the undisputed evidence demonstrates three unexpected results of Bayer's invention: (1) a 23-day regimen provides substantially greater ovarian suppression than a 21-day regimen even when the 21-day regimen contains a higher dose of EE; (2) even in missed pill situations a 24-day DSRP regimen provides greater protection than the same preparation in a 21-day regimen; and (3) even in real-world use, a 24-day DRSP product has superior efficacy to both a 21-day COC containing DRSP and a higher EE dose and to all other 21-day COCs with a higher EE dose without increasing the risk of adverse side affects.

2. Expert Skepticism of the Invention

FDA experts expressed doubts over whether the 24-day regimen would result in better contraceptive efficacy, and they were also skeptical of the safety profile in light of the increased monthly dose compared to Yasmin (which contains DRSP and 30 μg EE in a 21/7 regimen). The FDA informed Bayer that the application could only be approved if Bayer provided additional data "demonstrat[ing] a clinical benefit for the 24-day regimen over that provided by a 21-day regimen to offset the increased potential risk associated with the additional 3 days of [DRSP/EE]." (Ex. 40, 11/17/04 Griebel Letter.) Alternatively, the FDA suggested that Bayer propose a 21-day regimen, which shows that the conventional wisdom of 21/7 superiority arising from the prior art. Skepticism from experts in the field about the benefits of the invention is "relevant and persuasive evidence" of non-obviousness. Monarch Knitting Mach. Corp. v. Sulzer Morat GmbH, 139 F.3d 877, 885 (Fed. Cir. 1998). The undisputed evidence establishes that the claimed invention faced such skepticism.

3. Industry Praise for the Invention

Several articles have recognized the *Contraception* article reporting the results of Study AA51 as the first peer-reviewed publication reporting the surprising degree of ovarian suppression

from a slightly extended pill-taking regimen. (*See* Ex. 1, Sanfilippo Rep. 71-75)(citing Exs. 43-48). Even as late as 1999 experts in the field described the 24/4 regimen as an "innovative strategy." (Ex. 49, Sullivan 1999). Appreciation of the invention by those of ordinary skill in the art is further evidence that the invention was not obvious. Vulcan Eng'g Co. v. Fata Aluminum, Inc., 278 F.3d 1366, 1373 (Fed. Cir. 2002).

4. Copying of the Invention

It is also undisputed that Defendants—as well as manufacturers Teva and Lupin—copied Bayer's invention in an effort to seek FDA approval for their generic product prior to the expiration of Bayer's patent. Evidence that others copied the patented invention supports a finding of non-obviousness. Iron Grip Barbell Co. v. USA Sports, Inc., 392 F.3d 1317, 1325 (Fed. Cir. 2004); see also Stratoflex, Inc.v. Aeroquip Corp., 713 F.2d 1530, 1541 ("An alleged infringer's lauding of all the available art may . . . have a hollow ring when played against its disregard of that art and its copying of the invention.").

F. Summary

Under the four-part test for obviousness detailed in Graham, 383 U.S. at 17-18, the Court considered (1) the scope and content of the prior art; (2) the difference between the prior art and the claimed invention; (3) the level of ordinary skill in the art; and (4) any objective evidence of nonobviousness. Because the differences between the prior art and the claimed invention are substantial and the objective evidence of nonobviousness weighs heavily in Plaintiffs' favor, the Court finds that no genuine issues of material fact prevent the Court from granting summary judgment in Plaintiffs' favor and against Defendants.

V. Conclusion

Accordingly, IT IS HEREBY ORDERED that Defendants/Counter-claimants' Joint Motion for Summary Judgment (#252/253) is **DENIED**;

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IT IS FURTHER ORDERED that Plaintiffs' Motion for Summary Judgment of Non-obviousness of Claims 13 and 15 of United States Reissue Patent No. '564 (#254/255) is **GRANTED**;

IT IS FURTHER ORDERED that Bayer's Motion to Strike (#313) is **DENIED**.

DATED this 29th day of March 2012.

Kent J. Dawson
United States District Judge